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Review

Preventing congenital neonatal heart block in offspring of mothers with anti-SSA/Ro and SSB/La antibodies: A review of published literature and registered clinical trials☆,☆☆

Norbert Gleicher [a,b,*], Uri Elkayam [c]

[a] The Center for Human Reproduction, New York, NY 10021, United States
[b] Foundation for Reproductive Medicine, New York, NY 10021, United States
[c] Department of Medicine, Division of Cardiology, University of Southern California at Los Angeles, Los Angeles, CA 90033, United States

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ABSTRACT

Offspring of women with anti-SSA/Ro–SSB/La antibodies are believed to be at risk for congenital heart block (CHB). Whether this risk can be reduced, and what constitutes standard of care treatment is, however, unclear. The objective of this review therefore was to determine whether currently proposed standard of care treatments to avoid CHB in offspring of mothers at risk are evidence-based. To do so, we conducted a review of the literature under appropriate keywords and phrases in *Medline/PubMed* and *Google Scholar* for the years 2000–2013. Reference lists were further reviewed, and relevant manuscripts were pulled. We also reviewed *www.clinicaltrials.gov* for registered studies. In the absence of randomized prospective clinical trials, a meta-analysis was not feasible. We, therefore, reviewed lower evidence level studies individually. Risk of CHB actually appears more closely associated with general autoimmunity than, specifically, with SSA/Ro–SSB/La antibodies. This and other observations raise questions whether CHB is caused by passively transferred maternal autoimmunity, as is currently widely believed. Observational studies suggest the possible effectiveness of intravenous gamma globulin (IV-Ig) and hydroxychloroquine (Plaquenil) in reducing CHB-risk. Evidence for both is, however, inconclusive, and studies are biased in favor of hydroxychloroquine and against IV-Ig. Based on the review of the literature, current evidence of effectiveness for any treatment has to be judged as insufficient. Among the available treatment options, some considerations favor IV-Ig over hydroxychloroquine or, alternatively, suggest treatment with IV-Ig periconceptionally and into early gestation, with hydroxychloroquine added or replacing IV-Ig at approximately 10 weeks gestational age. Benefits for the utilization of steroid drugs are unclear. Since no treatment can be considered as established, prevention of CHB in offspring should be considered experimental, and performed under appropriate study conditions.

Contents

Abbreviations: CHB, congenital heart block; IV-Ig, intravenous gamma globulin.

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* Corresponding author at: The Center for Human Reproduction, 21 East 69th Street, New York, NY 10021, United States. Tel.: +1 212 994 4400; fax: +1 212 994 4499.
E-mail address: ngleicher@thechr.com (N. Gleicher).

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1. Introduction

Associations between maternal autoimmunity and congenital heart block (CHB) risk in offspring were first recognized in systemic lupus erythematosus (SLE) [1], and later with maternal SSA/Ro and/or SSB/La antibodies and Sjögren's syndrome [2,3]. How close an association really exists with SSA/Ro may have to be reassessed. In a recent cohort study the association with SSA/Ro titers was found not significant, while the association with SSB/La antibodies was [4].

Esscher and Scott's initial observation in the 1970s [1] suggested that CHB represented an in vivo model for passively transferred maternal autoimmunity, causing fetal tissue damage [5], already in the second trimester of pregnancy resulting in fibrosis and calcifications of atrio-ventricular and sino-atrial nodes and in the bundle of His [6]. Interestingly, the auto-antigen, β_2-glycoprotein, closely associated with anti-phospholipid antibodies, appears protective [7]. Tissue damage and fibrosis appear to be the consequence of excessive apoptosis, macrophage–fibroblast crosstalk and TGFβ expression. Once a complete 3rd degree block is established, pharmacological attempts at reversal have never been successful. 1st and 2nd degree blocks may still be reversible with treatment [8], suggesting that severe fibrosis has not yet occurred.

The observed association of maternal autoimmunity with neonatal CHB led to the hypothesis that maternal treatment may prevent cardiac conduction damage in offspring. Various therapeutic approaches have been reported (Table 1), including plasmapheresis [2,12,14], steroids [3,4,11,12,14], intravenous gamma globulin (IV-Ig) [3,10], beta-adrenergic agents [9], cyclophosphamide [12], extracorporeal immunoabsorption [13], azathioprine [14], and most recently hydroxychloroquine (Plaquenil) [4,15], as well as B cell depletion therapies [16].

Most have undergone only anecdotal utilization, often involving single case reports. The largest clinical experience exists with steroids, with use of IV-Ig and the utilization of hydroxychloroquine (Plaquenil). Alleged ineffectiveness and significant side effects have reduced the utilization of steroids [17,18]. Widely applied in medicine, offering hypothetical utility in multiple possible ways, considered safe and lacking significant side effects [19], IV-Ig became the treatment of choice over a decade ago [19]. Especially among rheumatologists, hydroxychloroquine has, however, more recently evolved as the preferred treatment. We in this study offer a systemic review of the subject, addressing the underlying hypothesis for preventive treatment of CHB, and how CHB can be prevented with currently available therapeutic means.

Table 1
Treatments proposed in the literature in attempts to prevent CHB.[a]

Treatment	Total n of reported patients	Reference
Plasmapheresis	3	[2,12,14]
Steroid drugs[b]	43	[3,4,11,12,14]
IV-Ig	9	[3,10]
B-adrenergic drugs	1	[9]
Cyclophosphamide	1	[12]
Extracorporeal immunoabsorption	2	[13]
Azathioprine	1	[14]
Hydroxychloroquine (Plaquenil)[b]	33	[4]
B cell depletion therapies	0	[16]

[a] Table does not include the 4 studies described in Table 2.
[b] Includes the recent study by Tunks et al., which utilized hydroxychloroquine or daily prednisone in a cohort study of 33 women.

2. Methods

We conducted a review of the English literature through *Medline/Pub Med* and *Google Scholar* for the years 2000–2013 under the following keywords and phrases: <congenital heart block>, <congenital fetal heart block>, <SSA/SSB antibodies>, <Ro/La antibodies>, <neonatal lupus>, <Sjögren's syndrome>, <congenital heart block in SLE>, <congenital heart block in Sjögren's syndrome>, <treatment of congenital heart block>, <intravenous gamma globulin and congenital heart block>, <hydroxychloroquine and congenital heart block>, <Plaquenil and congenital heart block>, <autoimmunity and congenital heart block>, <pregnancy and congenital heart block>, and <embryology of cardiac conduction system>. Reference lists of so found papers were further reviewed for additional relevant publications. One-hundred twenty-two publications were reviewed, among which 49 are referenced in this manuscript.

We also searched www.clinicaltrials.gov under the same keywords and phrases for relevant clinical trials, either in progress or already completed. Only two relevant clinical trials were listed. One was matched to an already published manuscript.

Since no prospectively randomized clinical trials were found, a meta-analysis was not feasible. Best available evidence was, therefore, derived from publications with lower evidence levels, which are individually reviewed.

3. Results: interpretation of published literature

Scott's group was the first to suggest that maternal treatment may alleviate risks of CHB in offspring [1]. Since not a single prospective clinical trial has been performed to this date to confirm the hypothesis, available potentially supportive clinical data are based on lower evidence levels. Whether this hypothesis, therefore, can be considered supported by enough evidence to warrant treatment of mothers at risk is, therefore, an important aspect of this review.

3.1. Pathophysiology of CHB

The hypothesis is supported by animal models, in which investigators produced autoantibody-induced CHB, up to complete 3rd degree block [20–26]. Most of these models employed SSA/Ro and/or SSB/La antibodies [20,24–26] or immunoglobulin fractions [22,23], also in the human clinical experience associated with CHB risk [27–30]. Indeed, anti-SSA/Ro antibodies have also been suggested to be arrhythmogenic in adults [31]. Other autoantibodies than SSA/Ro–SSB/La have also been associated with risk, though those associations in humans are less convincing, and animal models are lacking [26].

Demonstrated association of SSA/Ro–SSB/La in humans and in animal models proved, however, surprisingly weak. Indeed, in humans only as little as 2% of antibody-positive women will have affected pregnancies, though the risk increases at least 10-fold after an affected pregnancy [17]. This latter fact, and the observation that a large majority of mothers with affected offspring demonstrate SSA/Ro–SSB/La antibodies have been widely perceived as evidence for a pathophysiologic role of these antibodies in the occurrence of CHB.

Associations, however, in medicine do not always mean causation. The rarity of occurrence of CHB in association with SSA/Ro–SSAB/La is, indeed, difficult to explain if CHB, exclusively, were to be an antibody-mediated process. Co-factors for risk, either genetic or environmental in nature, have, therefore, been suggested. In a rat model,